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EXAMINER
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ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,193	NEYSES, LUDWIG	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/15/06, 07/31/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 14-23 are currently pending in the application.

Applicant's election with traverse to various species in the reply filed on 01/28/09 is acknowledged. The traversal is on the ground(s) that the claims relate to a single general inventive concept. Given that applicant has perfected their foreign priority claim to July 03, 2003, the Schuh reference is no longer applicable and therefore does not render the invention not related to a single general inventive concept. Moreover, in view of the unity of invention, the species election is also not applicable as unity of invention was not broken. Thus, the Examiner contends that unity of invention still exists among the species and therefore the requirement for species election is hereby withdrawn.

Thus, the requirement is still deemed proper and is therefore made FINAL. Claims 14-23 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the limitation "identifying a mutation or a post-translational modification of a gene encoding the PMCA4 isoform according to claim 14" in lines 1-3" of claim 23. However, there is insufficient antecedent basis for this limitation in the claim as the limitations of identifying a mutation or a post-translational modification appear nowhere in claim 14.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of achieving a contraceptive effect comprising administering a PMCA4 inhibitor thereby inhibiting sperm mobility, does not reasonably provide enablement for a method for diagnosing infertility in a human male comprising identifying a mutation or a post-translational modification of a gene encoding the PMCA4 isoform according to claim 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method for diagnosing infertility in a human male comprising identifying a mutation or a post-translational modification of a gene

encoding the PMCA4 isoform according to claim 14. The instant specification fails to provide information that would allow the skilled artisan to practice the diagnosis infertility in a human male comprising identifying a mutation or a post-translational modification of a gene encoding the PMCA4 isoform according to claim 14 especially given that the PMCA4 inhibitor is effective in inhibiting proteins while applicant is claiming identifying mutations and modifications in genes, two contrasting entities.

In re Sichert, 196 USPQ 209 (CCPA 1977)

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to diagnosing infertility in a human male comprising identifying a mutation or a post-translational modification of a gene encoding the PMCA4 isoform according to claim 14. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As previously argued, the examiner cites the fact that applicant is claiming identification of a mutation or post-translational modification in a gene using a protein inhibitor. Moreover, applicant failed to delineate exactly how such identification will occur using the PMCA4 inhibitor.

2. The breadth of the claims

The claims are thus very broad insofar as they recite the "utilization of a PMCA4 inhibitor not just at the protein level but rather at the gene level". While a protein can inhibit downstream expression of a gene for example at the mRNA and thus protein expression in a concentration- and time-dependent manner, applicant has failed to show how exactly is the PMCA4 inhibitor is involved in identifying a mutation or post-translational modification of the PMCA4 gene.

3. The amount of direction or guidance provided and the presence or absence of working examples

While the specification provides direction and guidance on how to determine possible mutations or polymorphisms, nowhere does applicant points out how the PMCA4 inhibitors are utilizing in such methods. No reasonably specific guidance is provided concerning useful therapeutic protocols for diagnosing mutations utilizing PMCA4 inhibitors. The latter is corroborated in the specification on page 11.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for identifying a mutation or a post-translational modification of a gene encoding the PMCA4 isoform by administering a

PMCA4 inhibitor. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-15 and 17-20 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Chaudhary et al. (Am. J. Physiol Cell Physiol. 2001, Vol. 280, pgs. C1027-C1030) in view of Wennemuth et al. (J. Gen. Physiol. June 30, 2003, Vol. 122, pgs. 115-128).

Chaudhary et al. teach that plasma membrane (PM) Ca2+ pump is a Ca2+ Mg2+-ATPase that expels Ca2+ from cells to help hem maintain low concentrations of cytosolic Ca2+ (see abstract). Additionally, Chaudhary et al. teach that the PM calcium pumps use the energy of hydrolysis of ATP to expel cellular Ca2+ (see pg. C1027, left

col., Introduction section). Moreover, Chaudhary et al. teach that the PM Ca2+ pumps are present in all mammalian cells suggesting that such pumps are also present in humans as well (see pg. C1027, left col., Introduction Section). Specifically, Chaudhary et al. teach that PM Ca2+ pumps are encoded by four PM Ca2+-ATPase genes (a.k.a. PMCA) whose sequences are conserved in the various isoforms (pg. C1027, right col.). Furthermore, Chaudhary et al. teach that the sequence of extracellular domain 401-413 in human PMCA1b is similar to the corresponding sequences in PMCA 4 supporting the notion that the PMCA inhibitor of Chaudhary et al. would necessarily inhibit PMCA4 (see pg. C1029, left col. Discussion Section, last paragraph). Particularly, Chaudhary et al. teach Caloxin 2A1 as a novel PM Ca2+ pump inhibitor selected for biding to the extracellular domain of PMCA (see abstract and pg. C1029, right col., paragraph 1). Chaudhary et al. teach that Caloxin 2A1 was dissolved in Krebs solution (i.e. carrier) which contains 115 mM NaCl, 5 mM KCl, 22 mM NaHC93, 1.7 mM CaCl2, 1.1 mM MgCl2, 1.1 kH2Po4, 0.3 mM EDTA, and 7.7 mM glucose (instant claim 20; see pg. C1028, left col., Contractility experiments, last paragraph).

Chaudhary et al. however do not specifically teach a method achieving contraceptive effect comprising a PMCA4 isoform inhibitor or a method for diagnosing infertility in a human male. Similarly, Chaudhary et al. do not teach that the PMCA4 inhibitor is performed as a single contraceptive event or as a repeated contraceptive event.

Wennemuth et al. teach that the spermatozoon is specialized for a single vital role in fertilization (see abstract). In fact, past studies show that Ca2+ signals produced by the opening of PM membrane channels initiate several events required for the sperm to reach and enter the egg but reveal little about how resting Ca2+ is maintained or restored after elevation (see abstract). This suggests that blocking such PM channels would necessarily prevent fertilization as inhibition of such PM channels would prevent the sperm from reaching the egg and thereby blocking fertilization. Importantly, Wennemuth et al. teach that the Ca2+ ATPase pump of the PM (PMCA) performs the major task of Ca2+ clearance (see abstract and pg. 120, right col., last paragraph). Additionally, Wennemuth et al. teach that like other excitable cells, mammalian spermatozoa (i.e. including human sperm; instant claims 18-19) possess multiple voltage-gated calcium channels and use Ca2+ signals to control physiological responses (see pg. 115, left col., Introduction). Particularly, Wennemuth et al. teach that calcium is considered a regulator of sperm motility, a participant in capacitation, and an essential second messenger for the acrosome reaction (i.e. a reaction that occurs when sperm is penetrating the layers of the oocyte during fertilization; see pg. 115, left col.). According to Wennemuth et al., the sperm PM depolarizes, Ca2+ channels open, Ca2+ enters, and the Ca2+-dependent acrosome reaction ensues (see pg. 115, left col.). Wennemuth et al. teach that four major Ca2+ clearance mechanisms exist in most animal cells including PMCA which exports cytoplasmic Ca2+ ion and imports one or two extracellular protons at the expense of ATP (see pg. 115, right col., paragraph 2). Additionally, Wennemuth et al. teach that carboxyeosin (instant claim 15)

was used in blocking PMCA in sperm cells but prevented the cells from KCL depolarization (see pg. 120, right col., top paragraph). Thus, inhibition of PMCA would necessarily result in a contraceptive effect as the acrosome reaction (i.e. sperm penetrating the egg or ovum) would necessarily be prevented (instant claims 14 and 23).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize Caloxin 2A1 to inhibit sperm PM since Wennemuth et al. teach that the Ca2+ PM pump is involved in the fertilization of human eggs by sperms. Moreover, one of ordinary skill in the art would have found it obvious to utilize the PMCA4 inhibitor caloxin 2A1 as either a single contraceptive event or as a repeated contraceptive event depending on the efficacy of the method as a contraceptive method. Thus, given the teachings of Chaudhary and Wennemuth, one of ordinary skill would have been motivated to utilize Caloxin 2A1 to inhibit PMCA4 inhibitor with the reasonable expectation of providing a method that is effective in preventing conception and effective in inhibiting fertilization.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al. (Am. J. Physiol Cell Physiol. 2001, Vol. 280, pgs. C1027-C1030) in view of Wennemuth et al. (J. Gen. Physiol. June 30, 2003, Vol. 122, pgs. 115-128) as applied to claims 14-15 and 17-20 above and in further view of ().

The Chaudhary and Wennemuth references are as discussed above and incorporated by reference herein. However, Chaudhary and Wennemuth do not teach oral, parenteral or coated mechanical contraceptive of the PMCA inhibitors.

Zimmerman teaches male contraceptive composition that can be administered orally (see abstract). Zimmerman also teaches that oral contraceptives are the most prominent chemical contraceptive agents; however, other chemical agents can be used in the form of creams, foams, gels and suppositories (see pg. 1, paragraphs 0003 and 0008). Of interest, Zimmerman demonstrated that contraceptive compositions can be made in various forms including oral, parenteral, or topical administration (see pg. 5, paragraphs 0060-0062).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to formulate the PMCA4 inhibitor composition of Chaudhary since Zimmerman teaches that contraceptive composition can be formulate as an oral, parenteral or topical application. Thus, given the teachings of Chaudhary, Wennemuth, and Zimmerman, one of ordinary skill would have been motivated to formulate the composition of the aforementioned method as an oral, parenteral, or topical formulation in view of the disclosure of Zimmerman with the reasonable expectation of providing a contraceptive method that can be easily administered.

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al. (Am. J. Physiol Cell Physiol. 2001, Vol. 280, pgs. C1027-C1030) in view of Wennemuth et al. (J. Gen. Physiol. June 30, 2003, Vol. 122, pgs. 115-128) as applied to claims 14-15 and 17-20 above and in further view of Papurt (U.S. 5,314,447).

The Chaudhary and Wennemuth references are as discussed above and incorporated by reference herein. However, Chaudhary and Wennemuth do not teach addition of conventional contraceptive device.

Papurt teaches the use of condoms and contraceptive devices as mechanical barriers (see abstract). Papurt further teach that condom barrier prophylactic devices and barrier contraceptive devices are generally known in the overall population, as well as the art, for their ability to prevent conception (i.e. a contraceptive product; col. 1, lines 17-20). According to Papurt, the more common types, involved male condoms or so-called female condoms positioned in such a way prior to sexual contact (see col. 1, lines 27-31). Moreover, Papurt teaches that condoms are known historically and have been in existence for centuries (see col. 1, lines 66-67 and col. 2, lines 17).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to further add the use of condom to the modified contraceptive method of Chaudhary since Papurt teaches the use of condom for preventing conception. Thus,

given the teachings of Chaudhary and Wennemuth, one of ordinary skill would have been motivated to add condoms to the contraceptive regimen of Chaudhary with the reasonable expectation of providing an enhanced contraceptive method that is not only effective in preventing conception but also effective against possible infections.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

04/03/2009

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617